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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/620,783	07/21/00	GREEN H	H0535/7012 /

EXAMINER

HM12/0810

NAFF,D

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ART UNIT	PAPER NUMBER
1651	8

DATE MAILED: 08/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/620783	Green et al
Examiner	**Group Art Unit**
Nafft	1651

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 7/21/00.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-26, 51, 57-77, 102, 117-119, 123-125, 135, 136, 143 + 144 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 1-26, 51, 57-77, 102, 117-119, 123-125, 135, 136, 143 + 144 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6 + 7 (filed 4/12 + 4/30/01)

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

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The preliminary amendment of 1/17/01 has been entered. The amendment canceled claims 27-50, 52-74, 78-101, 103-116, 120-122, 126-134 and 137-143.

Since there is no claim numbered 138, claims 139-145 have been renumbered as claims 138-144.

Claims examined on the merits are 1-26, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143 and 144.

Claim 135 is objected to because of the following informalities: the claim is objected to as being dependent on canceled claim 131. Appropriate correction is required.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25, 21, 22, 24, 25, 102, 117-119, 123-125, 135 and 136 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-25 are confusing and unclear by claim 1 requiring the presence of endogenous transglutaminase, and not being clear as to what the transglutaminase is endogenous to. In lines 1 and 3 of claim 1, it is suggested that -- containing endogenous transglutaminase -- be inserted after "surface", and in line 5 of the claims, before "endogenous" insert -- the --.

Where recited claims 21, 24, 102, 117-119, 123-125, 135 and 136, "glutamine-rich" and "lysine-rich" are uncertain as to meaning and scope. Being "rich" is relative and subjective.

Claims 22 and 25 are confusing and unclear by requiring a polymer to be selected from a group of materials that are not polymers. After "of" in line 2 of the claims, it is suggested that -- polymers containing -- be inserted.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-19, 23, 24, 26, 51, 75-77, 123-125, 135, 136, 143 and 144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al (5,490,980) in view of Bernstein et al (5,679,377) or Mathiowitz et al (5,271,961) and each taken with Won (5,145,675) (all listed on form PTO-1449).

The claims are drawn to a method of treating a subject by contacting the skin of the subject with microparticles having surface available transglutaminase substrate reactive groups, and in the presence of endogenous or exogenous transglutaminase covalently attaching the microparticles to the skin surface. Also claimed is a kit and composition containing the microparticles.

Richardson et al disclose attaching an active agent inherently containing or modified to contain an alkylamine ($R'NH_2$) group to skin, hair or nails by crosslinking the active agent through the alkylamine group to glutamine residues of skin, hair or nails (col 2, lines 44-68). The active agent may be an intact protein (col 3, line 4).

Bernstein et al disclose protein microspheres that can be made of a prolamine protein containing a high number of hydrophobic amino acids such as glutamine (col 5, lines 26-43). The microspheres can be formed entirely of protein or protein in combination with a polymer. The microspheres can have a size of about 50 to 100 nm to about 20 microns, and preferably from about 100 nm to about 5 microns (paragraph bridging cols 8 and 9). Composite protein-polymer microspheres can be formed by combining the protein with a non-protein natural or synthetic polymer (col 4, line 41 to col 5, line 24). The composite microspheres may be in the form of protein microspheres coated with a polymer or polymer microspheres coated with a protein. The protein can be modified chemically or enzymatically (paragraph bridging cols 6 and 7) to provide a property such as enhanced surface reactivity. Enhanced stability of the protein may be obtained by crosslinking the protein with transglutaminase (col 7, lines 11-22). The microspheres can be used for

delivery of a biologically active agent such as a drug to provide a desired release rate at a targeted site (col 3, lines 40-65). Microspheres containing a desired compound can be topically applied to skin or other areas to provide sustained delivery of the compound (col 10, line 1 to col 11, line 31).

Mathiowitz et al disclose the production and use of protein microspheres essentially as Bernstein et al.

Won et al disclose topically applying porous polymer microspheres containing an active substance to skin to provide controlled release of the active substance for prolonged activity on the skin (col 2, lines 42-50).

It would have been obvious to provide the active agent of Richardson et al in a protein microsphere and use transglutaminase to attach the protein microsphere to skin to provide release of the active agent at a desired rate as suggested by Bernstein et al or Mathiowitz et al and Won using protein or polymer microspheres to deliver an active agent at a desired release rate to a site such as skin. It would have been expected that transglutaminase will crosslink the glutamine of the protein microspheres with glutamine and/or amino groups of skin since it is known to crosslink protein with transglutaminase. When desiring glutamine groups for reacting with transglutaminase, it would have been obvious to omit treating the protein of the microspheres with transglutaminase for crosslinking to increase stability as may be carried out by Bernstein et al or Mathiowitz et al. Forming a kit as in claims 51 and 75-77 would have been obvious in view of Richardson et al disclosing (col 14, lines 5-12) providing a package containing an active agent and

transglutaminase. A composition as required by claims 123-125, 135 and 136 would have been obvious from the references since it would have obvious to provide the protein microspheres with sufficient surface glutamine groups to attach the microspheres to skin with transglutaminase. As to claims 143 and 144, it would have been obvious to use a non-nucleic acid active agent in the protein microsphere when the function of such an agent is desired, and selecting a preferred particle size within the ranges of Bernstein et al or Mathiowitz et al would have required only limited routine experimentation and been obvious. The limitations of dependent claims would have been matters of obvious choice within the ordinary skill of the art in view of the disclosures of the references.

Claims 2, 20, 21, 102 and 117-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1, 3-19, 23, 24, 26, 51, 75-77, 123-125, 135, 136, 143 and 144 above, and further in view of Zheng et al (c2 on form PTO-1449).

The claims require the transglutaminase substrate groups to be lysine.

Zheng et al disclose producing microspheres containing lysine amino groups to covalently link the microspheres to desired molecules. The microspheres are a blend of a poly(lactide-co-glycolide) and poly(ϵ CBZ-L-lysine).

When attaching protein microspheres with transglutaminase to skin as set forth above, it would have been obvious to provide the protein microspheres with lysine groups by blending the protein of the microspheres with poly(ϵ CBZ-L-lysine) as suggested by Zheng et al since

Richardson et al disclose reacting alkylamine groups with transglutaminase to provide attachment of an active agent to skin.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 123-125, 143 and 144 are rejected under 35 U.S.C. 102(b) as being anticipated by Bernstein et al or Mathiowitz et al.

The protein microspheres of Bernstein et al or Mathiowitz et al are inherently glutamine-rich, and inherently contain sufficient transglutaminase reactive substrate groups on their surfaces to attach the microspheres to skin in the presence of endogenous or exogenous transglutaminase as in claims 123-125. Crosslinking protein with transglutaminase as disclosed by Bernstein et al or Mathiowitz et al is optional and not essential. The microspheres of Bernstein et al or Mathiowitz et al can contain a non-nucleic acid active agent and have a particle size in the range of claims 143 and 144.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-26, 51, 75-77, 102, 117-119, 123-125, 135, 136, 143 and 144 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 6,267,957 in view of Berstein et al or Mathiowitz et al and each taken with Won.

The claims of the patent require attaching an agent to body tissue by applying to the body tissue a conjugate of the agent and a linking molecule such as a polymer containing glutamines or lysines in the presence of transglutaminase to crosslink the conjugate to the body tissue via the linking molecule.

For the type of reasons set forth above, it would have been obvious to substitute the conjugate containing an agent in the patent claims with protein microspheres containing the agent as suggested by Berstein et al or Mathiowitz et al and Won.

Claims 22 and 25 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 305-3014 or 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1651

DMN
8/9/01